Inspiratory resistance maintains arterial pressure during central hypovolemia: Implications for treatment of patients with severe hemorrhage

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Objective: **To test the hypothesis that an impedance threshold device would increase systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure and delay the onset of symptoms and cardiovascular collapse associated with severe central hypovolemia.**

Design: **Prospective, randomized, blinded trial design.**

Setting: **Human physiology laboratory.**

Patients: **Nine healthy nonsmoking normotensive subjects (five males, four females).**

Interventions: **Central hypovolemia and impending cardiovascular collapse were induced in human volunteers by applying progressive lower body negative pressure (under two experimental conditions: a) while breathing with an impedance threshold device set to open at -7 cm H_2O pressure (active impedance threshold device); and b) breathing through a sham impedance threshold device (control).**

Measurements and Main Results: **Systolic blood pressure (79 ± 5 mm Hg), diastolic blood pressure (57 ± 3 mm Hg), and mean arterial pressure (65 ± 4 mm Hg) were lower ($p < .02$) when subjects (n = 9) breathed through the sham impedance threshold device than when they breathed through the active impedance threshold device at the same time of cardiovascular collapse during sham breathing (102 ± 3, 77 ± 3, 87 ± 3 mm Hg, respectively). Elevated blood pressure was associated with 23% greater lower body negative pressure tolerance using an active impedance threshold device (1639 ± 220 mm Hg-min) compared with a sham impedance threshold device (1328 ± 144 mm Hg-min) ($p = .02$).**

Conclusions: **Use of an impedance threshold device increased systemic blood pressure and delayed the onset of cardiovascular collapse during severe hypovolemic hypotension in spontaneously breathing human volunteers. This device may provide rapid noninvasive hemodynamic support in patients with hypovolemic hypotension once the blood loss has been controlled but before other definitive therapies are available. (Crit Care Med 2007; 35:1145–1152)**

Key Words: hemorrhagic shock; lower body negative pressure; intrathoracic pressure; impedance threshold device; cardiovascular collapse

Hemorrhagic shock remains a leading cause of death worldwide in both civilian and combat trauma (1–3). One of the challenges to effective treatment is maintaining vital organ perfusion in the face of severe hypotension when intravenous access, intravenous fluids, drug therapies, and surgical intervention are not immediately available (4, 5). Specifically, a low systolic blood pressure (SBP <90 mm Hg) has been considered a good indicator of the need for lifesaving interventions and of mortality (6–9). It is therefore reasonable to suspect that application of an acute therapeutic intervention designed to maintain SBP after significant blood loss could improve patient survivability from hemorrhage by delaying the onset of circulatory shock until more definitive care becomes available.

During normal inspiration, intrathoracic pressure decreases, resulting in a decrease in atrial pressure and an increase in venous return (10). Greater negative intrathoracic pressure can be produced by applying resistance during spontaneous inspiration through an impedance threshold device (ITD) (11–13). The ITD was originally designed to improve circulation during cardiopulmonary resuscitation after cardiac arrest (12–14). In laboratory experiments, breathing through an ITD also increased stroke volume, cardiac output, and SBP in normovolemic, normotensive humans, suggesting that its use might be helpful

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Supported, in part, by funding from the United States Army Medical Research and Materiel Command Combat Casualty Research Program and by Cooperative Research and Development Agreements between the U.S. Army Institute of Surgical Research (USAISR) and Advanced Circulatory Systems, Inc. (CRDA No. DAMD17-02-0160).

Dr. Lurie is a co-inventor of the impedance threshold device and founded Advanced Circulatory Systems, Inc., to develop the device. He owns stock in the company and will benefit from sale of the device. Dr. Metzger is employed by Advanced Circulatory Systems, Inc., and holds stock options in the company. The remaining authors have not disclosed any potential conflicts of interest.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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DOI: 10.1097/01.CCM.0000259464.83188.2C

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 APR 2007	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Inspiratory resistance maintains arterial pressure during central hypovolemia: implications for treatment of patients with severe hemorrhage	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)	5d. PROJECT NUMBER
Convertino V. A., Ryan K. L., Rickards C. A., Cooke W. H., Idris A. H., Metzger A., Holcomb J. B., Adams B. D., Lurie K. G.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX 78234	

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**SAR**	**8**	

in hypovolemic situations (15). Indeed, use of the ITD increased cardiac output, systemic arterial blood pressure, and survival time in hemorrhaged pigs (16–18) and in humans made hypotensive by orthostatic challenges (11, 19, 20). We therefore designed the present investigation to test the hypothesis that inspiratory impedance created by spontaneously breathing through an ITD would result in elevated arterial blood pressure and increased tolerance to severe central hypovolemia in human subjects.

MATERIALS AND METHODS

Subjects. Nine healthy nonsmoking subjects (five males, four females) with mean ± SEM age of 31 ± 2 yrs, body weight of 69.4 ± 9.1 kg, and height of 173 ± 2 cm were recruited to participate. A complete medical history and physical examination that included a resting electrocardiogram and clinical orthostatic exam (supine/seated/standing consecutive blood pressure measurements) were obtained on each of the potential subjects. In addition, female subjects underwent an initial urine test before experimentation to ensure that they were not pregnant. Subjects maintained their normal sleep pattern, refrained from exercise, and abstained from caffeine and other autonomic stimulants such as prescription or nonprescription drugs for ≥48 hrs before each experimental protocol unless cleared by the physician medical screener to continue taking the medications. During an orientation session that preceded each experiment, all subjects received a verbal briefing and a written description of all procedures and risks associated with the experiments and were made familiar with the laboratory, the protocol, and procedures. Experimental procedures and protocols were reviewed and approved by the Institutional Review Board for the use of human subjects at the Brooke Army Medical Center at Fort Sam Houston, Texas. Each subject gave written informed voluntary consent to participate in the experiments.

Model of Central Hypovolemia. Lower body negative pressure (LBNP) was used in the present investigation as an experimental tool to simulate loss of central blood volume (e.g., hemorrhage) in humans (21). With the use of a neoprene skirt designed to form an airtight seal between the subject and the chamber, the application of negative pressure to the lower body (below the iliac crest) with the subject in a supine position results in a redistribution of blood away from the upper body (head and heart) to the lower extremities and abdomen (Fig. 1*A*). Thus, this model provides a unique method of investigating interventions such as the ITD under conditions of controlled, experimentally induced hypovolemic hypotension. Absolute equivalence between the magnitude of negative pressure applied and the magnitude of actual blood loss cannot at this time be determined, but review of both human and animal data reveals ranges of effective blood loss (or fluid displacement) caused by LBNP (21). Based on the magnitude of central hypovolemia, we have previously proposed that 10–20 mm Hg of negative pressure induces hemodynamic responses that are equivalent to those resulting from blood loss ranging from 400 to 550 mL; 20–40 mm Hg of negative pressure equates to blood loss ranging from 550 to 1000 mL; and >40 mm Hg of negative pressure induces hemodynamic responses that are equivalent to those resulting from blood loss approximating ≥1000 mL (21). We have also previously attempted to classify hemorrhage as mild, moderate, or severe and coordinate these descriptors with the magnitude of chamber decompression during LBNP; a thorough review of such comparisons can be found in our previous work (21), but we reproduce for convenience the primary results from our review in Fig. 2.

Experimental Intervention. The ITD (Advanced Circulatory Systems, Inc., Eden Prairie, MN) is a small (35 mL) lightweight disposable plastic airway pressure regulator that can be attached to a face mask or other airway adjunct. The ITD includes a specially designed valve that closes when the pressure within the thorax is less than atmospheric pressure and a second valve (termed the safety check valve) that opens at a preset negative intrathoracic pressure of approximately −7 cm H_2O. The ITD enhances the duration and magnitude of the small intrathoracic vacuum that develops with each inspiratory effort, thereby drawing blood from the extrathoracic venous system into the heart and lowering intracranial pressure (12, 13, 22). By increasing cardiac preload, the ITD results in an immediate increase in SBP and diastolic blood pressure (DBP) (23). There is little resistance (<2 cm H_2O) during exhalation. An ITD set at −7 cm H_2O was chosen because this level has been previously shown to be tolerable and effective in increasing arterial blood pressures in human volunteers (15, 24). Inspiratory and expiratory pressures were recorded directly from the ITD using a commercial pressure transducer (All

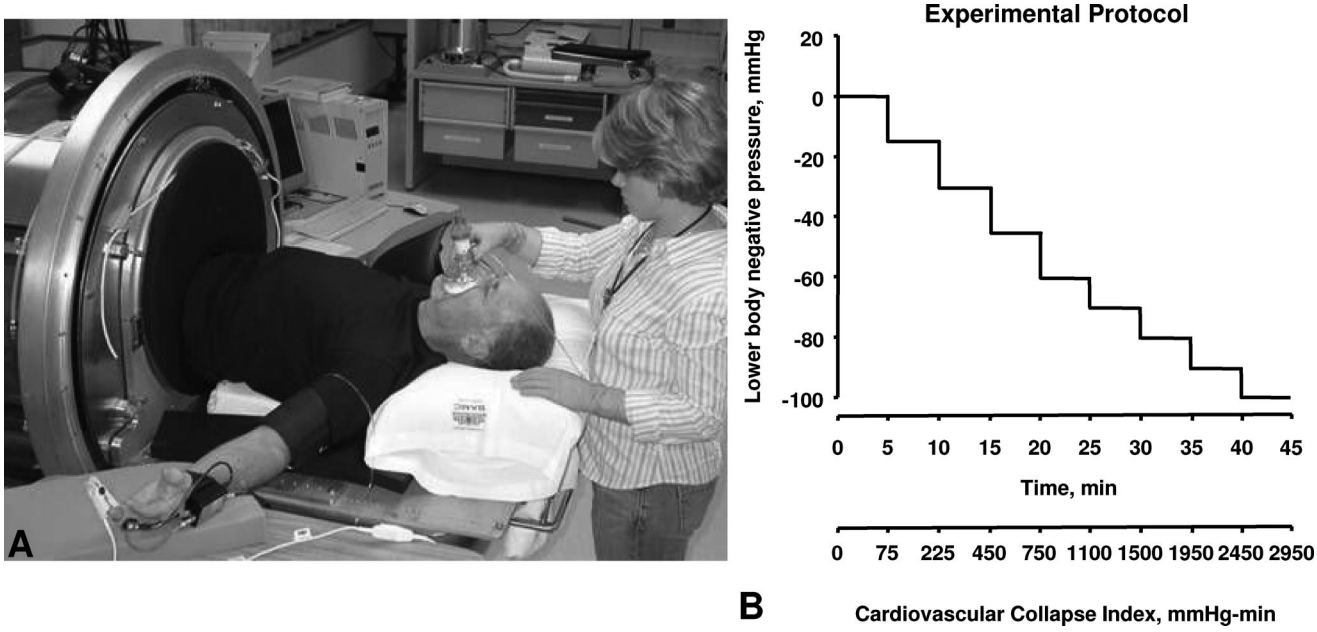

Figure 1. Subject in the lower body negative pressure (LBNP) device breathing through an impedance threshold device (*A*) and the LBNP protocol (*B*). Bottom abscissa indicates Cardiovascular Collapse Index corresponding to integrated product of time and LBNP level.

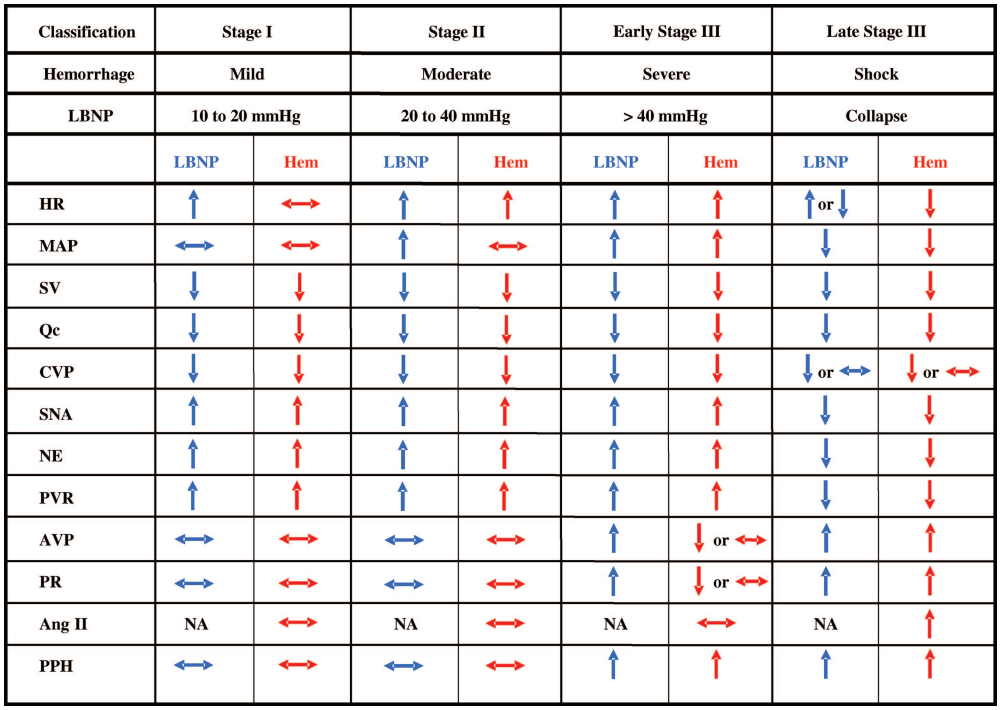

Figure 2. Comparison of global physiologic responses to hemorrhage (*Hem*) and lower body negative pressure (*LBNP*). *HR*, heart rate; *MAP*, mean arterial pressure; *SV*, stroke volume; Q_c, cardiac output; *CVP*, central venous pressure; *SNA*, sympathetic nerve activity; *NE*, norepinephrine; *PVR*, peripheral vascular resistance; *AVP*, arginine vasopressin; *PRA*, plasma renin activity; *Ang*, angiotensin; *PPH*, pancreatic polypeptide hormone. Modified from Cooke et al (21).

Sensors Corporation, Morgan Hill, CA) connected to the face mask.

Experimental Design. All subjects were instrumented with an infrared finger photoplethysmograph (Finometer Blood Pressure Monitor, TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands) and an electrocardiogram to record beat-by-beat arterial pressures and pulse rate. The Finometer blood pressure cuff was placed on the middle finger of the left hand, which in turn was laid at heart level. Excellent estimates of directly measured intra-arterial pressures during various physiologic maneuvers have been demonstrated with this device (25–28). Peripheral arterial oxygen saturation was measured with a standard pulse oximeter. Each subject underwent exposure to LBNP protocols designed to test his or her tolerance to experimentally induced hypotensive hypovolemia. The LBNP protocol consisted of a 5-min rest period (0 mm Hg) followed by 5 mins of chamber decompression to −15, −30, −45, and −60 mm Hg and additional increments of −10 mm Hg every 5 mins until the onset of cardiovascular collapse or the completion of 5 min at −100 mm Hg (Fig. 1*B*). Cardiovascular collapse was defined by one or a combination of the following criteria: a) a precipitous decrease in SBP >15 mm Hg; b) a sudden decrease in pulse rate >15 beats/min; c) progressive diminution of SBP <70 mm Hg; and d) voluntary subject termination due to onset of presyncopal symptoms such as gray-out, sweating, nausea, or dizziness. Subjects completed three experimental sessions: a) an initial protocol to determine LBNP tolerance without the application of any mask or valve devices (baseline LBNP tolerance); b) exposure to the LBNP protocol while spontaneously breathing through a face mask with an ITD set at a resistance of approximately −7 cm H_2O (active ITD); and c) exposure to the LBNP protocol while spontaneously breathing through the same face mask and valve without inspiratory resistance (sham ITD or control condition). The three experimental sessions were separated by a minimum of 2 wks to avoid the possibility of increased LBNP tolerance due to multiple exposures (29, 30). The ITD devices were placed on the subjects at one LBNP level lower than the level that produced cardiovascular collapse during the initial baseline tolerance protocol. The ITD was held in place by an investigator (Fig. 1*A*) in an effort to ensure an airtight seal while imposing minimal impact on the subject's hemodynamic responses. For example, a subject who experienced cardiovascular collapse at −60 mm Hg LBNP during the baseline tolerance protocol would begin breathing on the sham or active ITD at −45 mm Hg during the treatment experiments. The order of the two ITD treatments was randomized and counterbalanced so that five of the subjects underwent testing with active ITD treatment first, and four of the subjects underwent testing with the sham ITD treatment (control condition) first. All experimental protocols for a given subject were initiated at the same time of day.

Outcome Measures. The primary outcome measure was the Cardiovascular Collapse Index (CCI). Since central blood volume was progressively reduced with increased time of LBNP exposure with our protocol, we used the CCI as a well-established sensitive index that more adequately quantifies tolerance differences than a simple measure of LBNP exposure time (31, 32). For example, if LBNP tolerance was simply defined by absolute test time, completion of 4 mins of 60 mm Hg of LBNP (total test time = 24 mins) would represent a 9.1% higher tolerance compared with completion of 2 mins at 60 mm Hg of LBNP (total test time = 22 mins). However, when additional LBNP (i.e., reduced central blood volume) is factored with progressive time into the calculation of CCI, 4 mins at 60 mm Hg of LBNP (CCI = 690 mm Hg-min) represents a 21.1% higher tolerance compared with 2 mins at 60 mm Hg of LBNP (CCI = 570 mm Hg-min). CCI was calculated as the sum of the products of LBNP level (in mm Hg) and time at each LBNP level (minutes); that is, CCI = (15 mm Hg × 5 mins) + (30 mm Hg × 5 mins) + (45 mm Hg × 5 mins) + . . . + (n mm Hg × t mins) where n = final LBNP level and t = time at final LBNP level until cardiovascular collapse. The secondary outcome measure was blood pressure measured at the time of cardiovascular collapse.

Statistical Analysis. A Student's *t*-test statistic for repeated measures was used to compare the baseline and sham ITD LBNP tolerance times. A one-way (ITD condition) randomized block (subjects) analysis of variance for repeated measures was used for comparison of primary (CCI) and secondary (blood

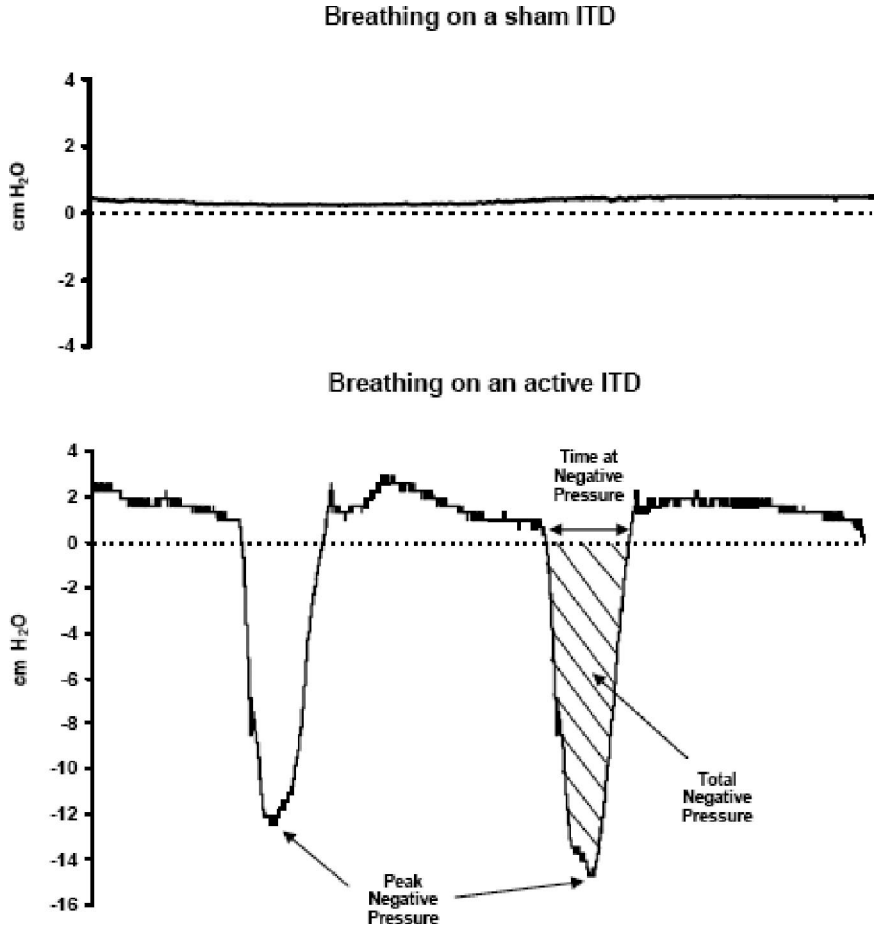

Figure 3. A representative pressure waveform during spontaneous breathing on a sham impedance threshold device (*ITD; top panel*) and on an active ITD device set at −7 cm H_2O (*bottom panel*). Total negative pressure is calculated as area under the curve; average negative pressure is calculated as total negative pressure divided by time at negative pressure. Average inspiratory time during breathing through the active ITD was 2.6 ± 0.3 secs compared with 2.0 ± 0.2 secs during breathing on the sham ITD.

pressure at time of cardiovascular collapse) variables across treatments (baseline, sham ITD, active ITD). This statistical model coincides with the experimental design in which all subjects acted as their own controls by being assigned to each of the experimental conditions. Arterial oxygen saturation data collected during the second minute of breathing on the active and sham ITD were compared using a paired two-tailed Student's *t*-test. Standard errors are presented as raw standard errors and were not adjusted for subject variation. Statistical probabilities are presented as the chances of concluding wrongly that the means of the two experimental ITD conditions are in fact due to true differences and do not arise from random variability for the given sample size of this experiment.

RESULTS

Subjects were normotensive with resting supine SBP, DBP, and mean arterial blood pressure (MAP) of 125 ± 5 mm Hg, 72 ± 3 mm Hg, and 92 ± 3 mm Hg, respectively. Figure 3 is a representative tracing of respiratory pressures generated from spontaneous breathing through a sham ITD (*top panel*) and an active ITD (*bottom panel*). Breathing through the sham ITD resulted in negligible pressure changes throughout the respiratory cycle. Conversely, inspiration through the active ITD produced a peak negative pressure of −12.2 ± 1.1 cm H_2O with an average negative pressure of −6.4 ± 0.7 cm H_2O. At the time of cardiovascular collapse, average inspiratory time and respiratory frequency with the active ITD were 2.4 ± 0.4 secs and 12 ± 1 breaths/min compared with 1.9 ± 0.3 secs and 14 ± 1 breaths/min with the sham ITD ($p \geq .297$). The nine subjects breathed through the active ITD for an average time of 896 ± 151 secs (14.9 ± 2.5 mins) without difficulty. Arterial oxygen saturation was 97.7 ± 0.3% during spontaneous breathing on the sham ITD and 98.4 ± 0.2% with the active ITD ($p = .03$).

Figure 4 is a representative tracing of beat-to-beat MAP obtained from one subject while breathing on a sham ITD (*top panel*) and active ITD (*bottom panel*) during the final 2 mins of LBNP exposure before LBNP termination. Respiratory excursions are apparent in both tracings, with elevations in MAP with each inspiration. The top panel demonstrates a gradual reduction in MAP from approximately 90 mm Hg to <60 mm Hg at the point of LBNP termination (approximately 2000 secs). In contrast, MAP is defended during inspiration on the active ITD throughout the same 2-min period (*bottom panel*), and cardiovascular collapse (i.e., decrease in MAP of <60 mm Hg) occurred after an additional 550 secs (>9 mins) and two additional levels of LBNP. The average blood pressures at the time of cardiovascular collapse were similar between experimental treatments (Table 1). However, arterial blood pressures were statistically higher ($p \leq .004$, Table 1) with the active ITD at the same time of the protocol in which subjects experienced cardiovascular collapse with the sham ITD.

The average time to cardiovascular collapse was 1878 ± 129 secs for baseline LBNP tolerance with no device compared with 1953 ± 106 secs during the sham ITD condition ($p = .757$). The average time to cardiovascular collapse was increased ($p = .024$) to 2156 ± 156 secs when subjects breathed through the active ITD. The average CCI for the group increased by 23% with the active ITD over that observed with the sham device (Table 1).

Kaplan-Meier analysis of LBNP test completion (labeled as survival on the y-axis) is presented in Figure 5. For the group of nine subjects, a CCI of 2010 mm Hg-min was associated with a completion rate of 0% when subjects breathed through the sham device, whereas breathing through the active ITD improved completion rate at this point to 44% (four of nine; chi-square = 8.534, $p = .004$).

DISCUSSION

In a patient who has lost a significant amount of blood volume, avoidance of cardiovascular collapse and impending circulatory shock depends on the ability to maintain adequate arterial blood pres-

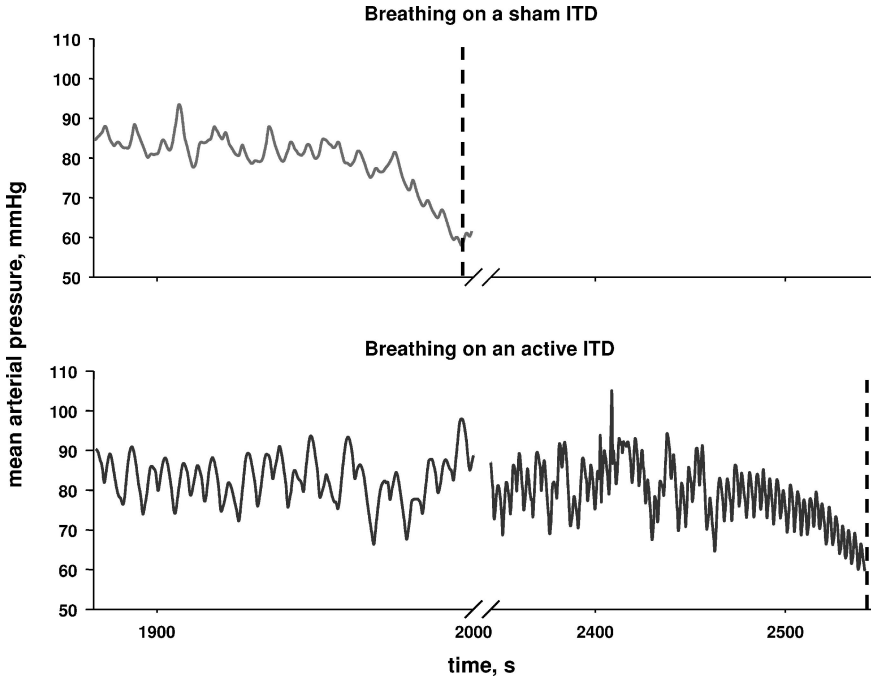

Figure 4. Representative tracings of beat-to-beat mean arterial blood pressure obtained from the same subject while breathing on a sham impedance threshold device (*ITD; top panel*) and an active ITD (*bottom panel*) during the final 2 mins of LBNP exposure before cardiovascular collapse. *Vertical broken line*, termination of lower body negative pressure.

Table 1. Systolic (SBP), diastolic (DBP), and mean (MAP) arterial blood pressures during spontaneous breathing through a sham impedance threshold device (ITD) at cardiovascular collapse (CC), through an active ITD at the time of CC with the sham ITD, and through an active ITD at CC

	Sham ITD CC	Active ITD vs. Sham ITD CC	Active ITD CC	F	*p*
CCI, mm Hg-min	1328 ± 144	—	1639 ± 220	2.908	.020
SBP, mm Hg	79 ± 5	102 ± 3[a]	81 ± 6	7.033	.004
DBP, mm Hg	57 ± 3	77 ± 4[a]	62 ± 5	7.189	.004
MAP, mm Hg	65 ± 4	87 ± 3[a]	70 ± 5	7.720	.003

CCI, cardiovascular collapse index.
[a]$p < .05$ compared with values for sham ITD CC and active ITD CC. Values are mean ± SEM.

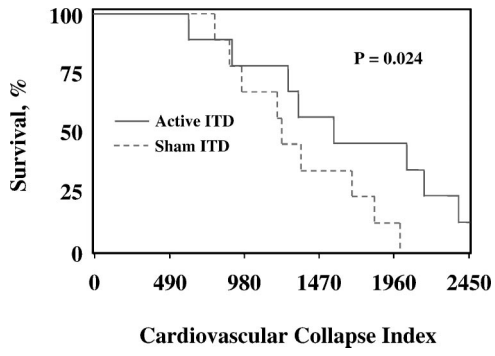

Figure 5. Lower body negative pressure completion (plotted as survival) curves of subjects treated with an active (*solid line*) and sham (*dashed line*) impedance threshold device (*ITD*).

sure in the presence of significant central hypovolemia. We introduced a model of progressive central hypovolemia leading to cardiovascular collapse (i.e., LBNP) in otherwise healthy human subjects to test the hypothesis that a valve designed to further decrease intrathoracic pressure during inspiration (the ITD) could effectively maintain arterial blood pressure and prolong tolerance to LBNP. Our index for tolerance to central hypovolemia (the CCI) was increased by an average of 23% when our group of subjects breathed through an active ITD. Our results are the first to demonstrate in humans that the time to cardiovascular collapse associated with progressive reduction in central blood volume and subsequent development of severe hypotension can be significantly improved by inspiratory resistance induced by spontaneous breathing through an ITD. These results complement similar findings in hemorrhagic shock in pigs (16–18). Taken together, these findings provide compelling evidence that mask ventilation with the ITD at the time of initial reductions in central blood volume may extend the therapeutic window of opportunity for resuscitation from hemorrhagic shock until definitive care is available.

With our experiment, we were able to demonstrate that cardiovascular collapse occurs reproducibly at an average blood pressure of approximately 80/60 mm Hg. This hemodynamic threshold for collapse defined in our LBNP model of progressive central hypovolemia coincides closely with the clinical value of SBP <90 mm Hg that is associated with the need for a lifesaving intervention (6–9). Using an ITD, we tested inspiratory impedance as an intervention for relieving hypovolemic hypotension. We found that breathing through the active ITD maintained arterial blood pressures >100/75 at the same level of central hypovolemia that caused cardiovascular collapse when the same subjects breathed through a sham ITD. Consequently, inspiratory impedance improved tolerance of our subjects to an acute reduction in central blood volume from 0% to 44% in terms of both LBNP exposure time and level of central hypovolemia (i.e., significantly greater CCI). Our results suggest that the ITD could potentially be a lifesaving intervention when used with patients suffering from life-threatening hemorrhage.

We previously reported only an acute and modest (7 mm Hg) elevation in SBP in healthy normovolemic, normotensive subjects when breathing on the ITD in the supine position with an uncompromised condition of optimal venous return (15). We hypothesized that even larger elevations in SBP may be produced by resistance breathing under conditions such as hemorrhage when venous return is compromised (15). The results from the present experiment support this hypothesis by demonstrating an average el-

evation in SBP of 23 mm Hg when estimated central blood volume was reduced by >2 L (21).

Hemostasis is the primary step to stabilize the hemodynamic effects caused by severe hemorrhage. However, it is also paramount to maintain adequate perfusion pressures to vital organs to avoid the development of hemorrhagic shock and ultimately death. The balance between maintaining both hemostasis and adequate arterial blood pressure is challenged by an increased risk of dislodging clots and exacerbating bleeding when interventions that elevate arterial blood pressure are applied following hemorrhage. In a swine hemorrhage model, the average SBP, DBP, and MAP points associated with rebleeding from an aortic wound were 94 mm Hg, 45 mm Hg, and 64 mm Hg, respectively (33). Although our subjects remained significantly hypotensive while breathing through the active ITD (SBP = 102 mm Hg) relative to their baseline blood pressure (SBP = 125 mm Hg), their pressures remained significantly higher than those identified with rebleeding in the swine model. Thus, application of the ITD, as with any other intervention designed to elevate perfusion pressure, may be most appropriate when used on patients with compressible wounds that allow for stable hemostasis.

Application of the ITD may also be effective during bleeding when hypotension is so severe that the elevation in blood pressure caused by breathing with inspiratory resistance remains below the threshold for dislodging clots. This notion is supported by a recent case of a soldier with a gunshot wound to the pelvis. The patient was admitted to a Combat Surgical Hospital in shock with an intra-arterial blood pressure of 36/16 and base deficit of 26. Although an arterial catheter was in place, the attending medical personnel experienced difficulties with placing a central venous catheter, the standard route for fluid resuscitation for combat casualties. Therefore, no blood or intravascular fluids were administered for 13 mins. Epinephrine, vasopressin, and atropine were administered via an endotracheal tube without success in raising blood pressure. An ITD was then applied, and a palpable intra-arterial blood pressure >70 mm Hg was achieved within minutes. The attending surgeon was able to place a central venous catheter and administer >16 units of blood (6 units of whole blood). Following damage control surgery, the patient was admitted to the operating room in a stabilized condition and survived to the next echelon of care.

Although the individual times to cardiovascular collapse were increased in eight of our subjects, one subject demonstrated an arterial blood pressure of 55/42 at 23.1 mins with the active ITD compared with 56/40 at 25.5 mins with the sham ITD. This result reflects our previously reported observations (34) that there are some conditions or individuals in whom the effect of the ITD is not always positive, a finding that has also been observed in hemorrhaged pigs (18). We have hypothesized that the absence of a protective effect against hypotension during ITD breathing in some subjects may result from ineffective breathing mechanics (33, 34). As such, when we examined measures of breathing mechanics in our cohort of subjects, we found that the one subject who did not benefit from the ITD generated the least amount of negative pressure upon inspiration (−3.5 cm H_2O vs. the group average of −6.4 cm H_2O). Perhaps more significant, this subject generated less negative pressure (−2.9 cm H_2O) just before the onset of cardiovascular collapse whereas the eight subjects with positive ITD effects generated more negative pressure (−7.8 cm H_2O) at this point in time. It may be that different individuals will benefit more from an ITD with different or variable cracking pressures. Severe hypovolemia can be associated with rapid, shallow breathing. Transforming ventilatory effort into more effective breathing to move air and blood underlies the mechanism and effectiveness of the ITD. The variation in mean arterial pressure shown in Figure 4 may reflect a shallow, rapid breathing pattern near the time of cardiovascular collapse. However, analysis of inspiratory time and respiratory rate suggests that breathing pattern at the point of cardiovascular collapse is not affected by the ITD and that most subjects can further reduce negative intrathoracic pressure with progressive reduction in central blood volume. This results in a significant increase in venous preload and cardiac output in animal models (17). These results underscore the important contribution of breathing mechanics in providing a positive ITD effect through generation of a minimum level of negative pressure, thereby optimizing the patient-powered thoracic pump mechanism that underlies the function of the ITD.

Although our healthy subjects tolerated the use of the ITD under conditions of severe central hypovolemia, we do not know all of the potential implications of ITD application in critically injured trauma patients. There is always the question of whether patients will be able to breath through the ITD given the increased work of breathing. In patients suffering from hypovolemic hypotension during renal dialysis, blood donation, or orthostatic hypotension, ITD use resulted in elevated blood pressure while the patients tolerated the increased work of breathing (20). The work of breathing through the ITD has been measured and was not found to be excessive (35). Between 4 and 8 J/min is required for normal breathing, whereas 12–16 J/min is required to breathe through the ITD (35). The data from the present study indicate that breathing through the ITD does not cause shallow, rapid breathing or negatively affect oxygen saturation. Thus, the ITD could be applied to all patients who are hypotensive but still able to breathe spontaneously. However, if patients have very low respiratory rates or rapid shallow breathing, they will not be able to tolerate the ITD and it should not be used. One advantage of the ITD in the hypotensive patient is that it can be immediately removed if it is not tolerated or if its use results in an excessive elevation in blood pressure. Finally, with positive pressure ventilation, the effects of the ITD are not diminished if patients can also take some breaths on their own. Thus, a patient who requires some assisted ventilation may benefit. The ITD will not work, however, in a patient who requires 100% positive pressure ventilation. For such patients, an intrathoracic pressure regulator will eventually be available for clinical use (36, 37).

Our experiment is not without limitations. First, we designed the protocol with a sham device and counterbalanced the order of treatments in an effort to control the experimental effect of breathing through a mask and valve apparatus. Although we could not remove the possible impact of the subject detecting the difference between breathing with inspiratory resistance (active ITD) and breathing with no resistance (sham device), we found no statistical difference when we compared the average LBNP tolerance time in the nine subjects when they breathed through a sham mask and

valve (~32.5 mins) with that in the same subjects when they had no mask and device (~31.3 mins). Thus, our data suggest that subjective recognition of the presence or absence of inspiratory resistance had a negligible impact on the experimental outcome. Second, the relatively short amount of time (~200 secs) that the ITD increased LBNP tolerance may have underestimated the potential to extend a patient to definitive care and, therefore, cannot be extrapolated to a clinical setting. Our protocol simulated a continuous hemorrhage since we continued progressive reduction in central blood volume by increasing LBNP following ITD application. As with any hemorrhagic trauma, the effectiveness of an intervention depends on stopping the bleeding. Future experiments will be required to determine whether the use of an ITD with a set level of central hypovolemia (analogous to obtaining hemostasis) would significantly extend the time to cardiovascular collapse. Third, the volunteers who used the ITD in our study were healthy subjects. Although we have no data on systemic oxygen sufficiency during LBNP exposure (e.g., lactates, mixed venous oxygen saturations), our subjects expressed no adverse effects of increased respiratory effort with the ITD when used in this model. However, it remains unclear whether the ITD will be tolerated by patients in hemorrhagic shock. The latter two issues require verification in clinical settings with patients suffering moderate to severe hemorrhage.

At the present time there are no clinical therapies, with the exception of intravenous fluids and intravenous vasopressor drugs, that acutely increase blood pressure in states of hypovolemic hypotension. Intravenous access and fluids, however, are not always readily available. On the battlefield, immediate intravenous resuscitation is not always feasible inasmuch as the combat medic may be under fire or in other circumstances that preclude starting an intravenous catheter. The results of the present investigation suggest that application of an ITD during the early stages of controlled hemorrhage may restore blood pressure and perfusion to vital organs. Although the device is not a panacea, we believe that these experiments demonstrate that the ITD may help to "buy time" until intravenous access is obtained and fluid resuscitation is begun or may be used as an adjunct to conventional resuscitative therapy, thus increasing the likelihood that the casualty can be stabilized and survive to reach a higher echelon of care. It is in this manner that we believe the ITD may provide a critical bridge to enable more definitive repair of the primary injury and ultimately save lives.

ACKNOWLEDGMENTS

We thank the subjects for their cheerful cooperation; Gary Muniz for his engineering and technical assistance during the experiments; and Dr. John McManus for his assistance with physical examinations and medical monitoring of the subjects during the experiments.

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